REMARKS

Applicants respectfully request entry of amendments to claims 12 and 13. Support for the amendments can be found throughout the specification, including Examples 5, 7, and 8, Figure 3, and the originally filed claims and, therefore, do not add new matter.

Applicants submit that pending claims 12-19 are in condition for allowance, or are in better condition for presentation on appeal, and respectfully request that the claims as amended be entered.

Objection

Applicants have provided herewith a corrected claim 13, where "truncation" has been replaced by --truncated--.

For these reasons, Applicants respectfully request that objection be withdrawn.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 12-19 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite.

Applicants traverse the rejection as it might apply to amended claim 13, including claims dependent therefrom, for the reasons given below.

Claim 12 no longer recites "ALT promoter" so this aspect of thee rejection is rendered moot. Applicants have amended the claim to recite "5' ALT gene" and "wherein hypermethylation of a 5' CpG island in the first exon of the p16 gene" in accordance with the suggestion offered in the Action. As such, one of skill in the art would understand the metes and bounds of the term.

Regarding the term "second product" as recited in claim 13, while Applicants do not acquiesce to the reasoning offered in the Office Action, in order to expedite prosecution toward allowance, claim 13 has been amended to clarify the antecedent basis of the term.

Regarding the term "the p16 gene product" as recited in claim 13, while Applicants do not acquiesce to the reasoning offered in the Office Action, in order to expedite prosecution toward allowance, claim 13 has been amended to clarify the which region of p16 is truncated.

For these reasons, Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 12-19 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written description support.

Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

The Office Action alleges, in pertinent part, that the specification does not disclose "5' ALT promoter region of the p16 gene," truncated p16 gene product," "the presence of hypermethylation of the 5' ALT promoter of the p16 gene is associated with the presence of any truncated p16 product," and "addition of the demethylation agent in step a".

While not acquiescing to the reasoning offered in the Action, in order to expedite prosecution toward allowance, Applicants have amended the claims to include elements which find clear support in the specification as filed.

For example, the Action itself recites that the instant specification discloses 5' ALT gene (at p. 3, Item 9). Further, a truncated p16 product lacking exon 1 is expressly recited at page 9, ll. 20-22 and Example 5. Also, "hypermethylation of a 5' CpG island in the first exon of the p16 gene is associated with the presence of the truncated product" and the demethylation step find direct support in Figure 3 (identifies that 5' CpG for p16 is within exon 1); Example 9; and at p. 9, ll. 17-19, which states:

> "Initial studies in the present invention revealed that de novo methylation of a CpG island that extends into exon 1 of p16 in cell lines and primary tumors is precisely associated with transcriptional block of full length p16. Reversal of methylation with 5'-azacytidine resulted in reexpression of p16 message."

Therefore, the amended elements do not add new matter. For these reasons, Applicants respectfully request that the rejection be withdrawn.

Claims 12-19 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

The Office Action alleges, in pertinent part, that the specification is not enabling a) for any (and all) fragments of exon 1 and exon 2; b) in that it is not clear that 5' ALT promoter is the same as 5' ALT gene; c) contacting the sample with a demethylating agent and demethylating agent added after extension; d) all degrees of methylation of the p16 gene; and e) for any (and all) methylation indicative of any and all neoplasms.

As the amended claims no longer recite "5' ALT promoter," this aspect of the rejection is rendered moot. However, Applicants respectfully submit that the above allegations are incorrect.

Applicants submit that the specification discloses that there is a difference between p16 products that can be used to amplify select amplicons from normal and neoplastic cells (e.g., p. 6, ll. 3-7). Further, the specification teaches that p16 in neoplastic cells lack sequences for exon 1, yet retain sequences for exon 2. The specification provides sequence information for both exons, as well as the complete sequence for the p16 gene (which was also known in the art at the time the instant application was filed). Also, the specification identifies where the truncated p16 is delimited due to insertion of the 5' ALT gene into exon 2 (e.g., p. 11, ll. 11-26). Thus, there is sufficient guidance to identify which fragments can be used to amplify select regions of the p16 gene necessary to practice the invention as claimed. Applicants submit that it is well within the abilities of the skilled artisan in the biotechnology arts to design primers to any of the sequences identified in the instant application for the 5' ALT gene, exon 1 of p16, and/or exon 2 of p16 to amplify a sequence such that the primers would detect the presence or absence of a particular amplicon.

Regarding timing for addition of the demethylating agent, the Action states that the agent can be added after extension because it is added during the same step of amplifying nucleic acid regions. Applicants respectfully submit, it is unclear as to why the Action has come to the position that this can not be done. For example, if one of skill in the art wanted to know what the affect of the demethylating agent was on the cells, amplification could be carried out before

agent contact and after agent contact on the same batch of cells, all in the same step as stated in the claims "under conditions suitable for primer extension of the complementary sequences." Such a sample could be a suspension of neoplastic cells, as neoplastic transformation is known in the art to generate cells that no longer adhere to substrata. Regarding degree of methylation, while it is possible that some inoperative embodiments may be embraced by the claims, this does not, *per se*, result in non-enablement (see, e.g., Atlas Powder Co. v. E.I. du Pont Nemours & Co., 224 U.S.P.Q. 409 (Fed. Cir. 1984)), and it is not the function of claims to specifically exclude possible inoperative embodiments (Id.).

Further, in response to what seems to be regarded as contradictory by the Action with respect to methylation and the presence of the truncated product between claims 12 and 13, claim 13 uses functional language to describe that if demethylation results in the second amplification product being detectable, this is due to methylation of the 5' CpG island in the first exon, where the effect of such methylation results in a truncated p16 gene product lacking exon 1. Thus, there is no contradiction.

As asserted by the Action, the specification discloses that discrete regions of CG dinucleotides (CpG islands) are unmethylated in normal cells and methylation of the 5' regulatory regions lead to transcriptional repression (p. 3, ll. 22-23). As stated above, the claims now recite "hypermethylation of a 5' CpG island in the first exon," and it is hypermethylation at this exon which is associated with truncation of the p16 gene product/transcriptional repression (p. 9, ll. 17-19). Thus, discrete regions are delimited by the claim, which region, as admitted by the Action, are frequently associated with cell lines and primary tumors of common neoplasms (p. 10, first paragraph).

As the claims embrace reversal of truncation by demethylation, which is ubiquitously associated with neoplastic cells that can be detected by the method as claimed (e.g., breast cancer, colon cancer, lung cancer, head and neck tumors), the amended claims do not embrace any (and all) neoplasms as alleged in the Action.

While it is appropriate to recognize variability in determining the scope of invention, determination of what is needed to support generic claims to biological subject matter depends on a variety of factors including 1) knowledge in the particular field, 2) the extent and content of

the prior art, 3) the maturity of the science or technology, and 4) the predictability of the aspect at issue. Capon v. Eshhar, 76 U.S.P.Q.2d 1078, 1084, 418 F.3d 1349, at 1356 (Fed. Cir. 2005).

The present invention represents more than "a mere germ of an idea," the specification supplies the novel aspects of the invention, and methylation determination is certainly not in the early stages of development (e.g., p. 3, l. 18 bridging to p. 4, l. 5). (See, also, Genentech, Inc. v. Novo Nordisk, 42 U.S.P.Q.2d 101, 108 F.3d 1361 (Fed. Cir. 1997)). Further, in the present specification, not only are the general teachings of how to select the requisite primers provided (e.g., p. 32, l. 14 bridging to p. 23, l. 2), but also specific examples are provided for use of such primers as claimed (e.g., Example 1, Item 2 ("Inverse PCR"); Item 3 ("RT-PCR"); Item 5 ("Primer extension assay"); Item 8 ("TNT assay"); Example 6; Example 7; Example 8; and Example 9). Moreover, standardized methods for practicing the invention are disclosed (e.g., p. 30, ll. 8-20). And while such procedures involve some level of technical manipulation, because such methods and steps are routinely used in the art, such procedures do not rise to the level of undue experimentation. (See, e.g., Johns Hopkins University v. Cellpro, Inc., 47 U.S.P.Q.2d 1705, 152 F.3d 1342 (Fed. Cir. 1998), where the court stated that "experimentation does not constitute undue experimentation" where "it is merely routine.").

Regarding unpredictability, it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize the generic invention. See, e.g., In re Angstadt, 537 F.2d 498, 504 (CCPA 1976). Accordingly, generic inventions are not *per se* invalid because success for each possible iteration is not assured. Capon, at 1357.

Regarding the Wands factors, 1) sequence information for each exon of p16 was known in the art; 2) the sequence for 5' ALT is provided in the specification as filed; 3) as stated above, methylation determination is certainly not in the early stages of development; 4) the level of skill in the art is high, and such a skilled artisan would have the knowledge and capabilities of using the information provided in the specification to make and use the invention commensurate in scope with the amended claims (e.g., identify regions within p16 exons to design primers for amplification, design probes for Southern blots, determine when to add demethylation agents for specific experimental uses, etc.); 5) the specification provides examples of use of the method

with a number of cells lines and tumor samples from human subjects (see, e.g., Example 11 and Table 2); 6) as stated above, standardized techniques for selecting the requisite primers (e.g., p. 32, l. 14 bridging to p. 23, l. 2), including specific examples for use of such primers as claimed (e.g., Example 1, Item 2 ("Inverse PCR"); Item 3 ("RT-PCR"); Item 5 ("Primer extension assay"); Item 8 ("TNT assay"); Example 6; Example 7; Example 8; and Example 9) are provided in the specification as filed. Moreover, standardized methods for practicing the invention are disclosed (e.g., p. 30, ll. 8-20) to provide direction to the skilled artisan; 7) at least 12 working examples of various aspects of the method as claimed are disclosed; and 8) as stated above, the procedures used to practice the invention are merely routine, and such procedures do not rise to the level of undue experimentation.

Therefore, the claims are enabled because the specification provides appropriate guidance, working examples, and prediction of function based on observed properties of the target gene such that one of skill in the art could practice the invention as claimed, in the absence of undue experimentation.

For these reasons, Applicants respectfully request that the rejection, including as it may be applied to the amended claims, be withdrawn.

Conclusion

Applicants submit that pending claims 12-19 are in condition for allowance, or are in better condition for appeal. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this submission.

Please charge Deposit Account No. 07-1896 in the amount of $760.00 for a Three Month Extension of Time fee and a Notice of Appeal fee. No additional fees are deemed necessary with the filing of this paper. However, the Commissioner is hereby authorized to charge any fees required by this submission, or credit any overpayments, to Deposit Account No. 07-1896 referencing the above-identified docket number.

Respectfully submitted,

Date: September 12, 2007

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